IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: K. Edwards

U.S. Serial No.: 10/034,981

Filed: December 27, 2001

For: *Intravenous Valproate for Acute Treatment of Migraine Headache*

Attorney Docket No.: NRI-001CN

Group Art Unit: 1618

Examiner: Fubara, B.

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REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

In response to the Examiner's Answer dated June 30, 2005, Appellants submit further remarks with respect to "Arguments" (subsection VIII) which are responsive to Examiner's Answer and are supplemental to the remarks already made of record in subsection VIII of the Appeal Brief filed on June 21, 2004.

ARGUMENTS

Rejection of Claims 1-14 Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1-14 under 35 U.S.C. §103(a) as being unpatentable over Welch ("Drug Therapy; Drug Therapy of Migraine." The New England Journal of Medicine) in view of Walser (U.S. Patent No. 5,432,176).

In maintaining her rejection of the pending claims, the Examiner has taken the position that regimens for acute migraine treatment and those for the preventative treatment of migraine are interchangeable. The Examiner may even be suggesting that acute treatment of migraine and migraine prophylaxis are one in the same treatment. For example, the Examiner states that the discussion in Welch "implies the presence of migraine headache at the time preventative treatment is instituted". In keeping with this flawed understanding of migraine treatment, the Examiner identifies one member of a class of compounds, the non-steroidal anti-imflammatory drugs (NSAIDS), which is described in Welch as having effectiveness in both migraine prophylaxis and acute migraine treatment. The Examiner then concludes that a very different compound, valproic acid, would be an obvious acute migraine treatment as Welch teaches its use in migraine prevention. In order to reach the intravenous administration of this compound as required by the instant invention, the Examiner provides an epilepsy reference in which valproate is administered by intravenous injection. The Examiner states that the skilled artisan would be motivated to administer valproate according to Walser in treating migraine because the "parenteral mode of administration would get valproate quicker to the blood stream."

The Examiner misreads Welch and ascribes motivation to the skilled artisan where there would be none. Clearly, while the indications are related, they are two distinct indications with quite different treatment regimes. Drugs used for the preventative treatment of migraine are not interchangeably used for the acute treatment of migraine. Drugs administered prophylactically to prevent migraines in persons with recurring and intense migraine headaches are not indicated for the clinical setting in which a patient having an acute migraine attack is treated. Likewise, drugs used to treat migraine attacks in the acute setting are not indicated for migraine prophylaxis. In fact, drugs used for preventative treatment are unsuitable and, often contraindicated for acute treatment, and visa versa.

This is due, at least in part to the different mechanisms of actions of the various classes of drugs used in migraine therapy. Although not all of the mechanisms are understood, in general, the acute treatment drugs act on mechanisms involved during a migraine attack. On the contrary, preventative treatment drugs act on mechanisms that cause, or that occur before, migraine attack. Of the known mechanisms discussed in Welch, the two different classes of drugs act on different receptors. For instance, on p. 1479, Welch explains that acute treatment drugs sumatriptan and ergotamine act presynaptically to block the neuropeptide-mediated inflammatory response after trigeminal stimulation (release of peptides from sensory axons of the trigeminal nerve supply which promotes local vasodilatation during a migraine attack). Sumatriptan and ergotamine may also act to block transmission in trigeminal neurons (see p. 1479). Furthermore, sumatriptan and ergotamine have known selectivity for the 5-HT_1 receptors on intracranial vessels. In contrast, preventative treatment drugs act on mono-amine-receptor sites (see p. 1479, left column). Preventative treatment drugs methysergide and amitriptyline are thought to "prevent migraine by blocking 5-HT_2 receptors on cerebral vessels and central neurons" (see p. 1480). Calcium-channel-blocking drugs are thought to "prevent vasoconstriction and 5-HT release" (see p. 1481). Because different receptors and vessels are implicated in acute migraine treatment versus prevention of migraine, one skilled in the art at the time of the invention would not have expected preventative drugs to be suitable for acute treatment of migraine.

Moreover, the skilled artisan would appreciate that of all the drugs described in Welch as suitable to the preventative treatment of migraine, only propranolol, atenolol and sodium divalporate (the salt of valrpoic acid) are FDA approved and all three are useless in the acute treatment of migraines. In fact, propranolol, which can be taken daily as an oral medication as preventative therapy is ineffective whether administered orally or intravenously during migraine attack. Likewise, atenolol is widely used for the prevention of migraine and is available as an IV preparation but is useless for acute migraine treatment

Even the NSAIDs listed in Welch as suitable for both preventitive and acute treatment of migraine are not, in fact, used by the skilled artisan for the routine treatment of these quite different indications. Notably, neither aspirin nor naproxen are FDA approved for either indication. When used chronically, aspirin and naproxen

both create the condition of "analgesic rebound headaches" and are, therefore, not used for more than a very short period of time as a migraine preventative. Excedrin (a combination of caffeine, aspirin and acetomenophen) is FDA approved for acute migraine treatment but increases migraine headaches when used regularly by causing chronic daily headaches via analgesic rebound.

Thus, even the NSAIDs (and/or general analgesics) mentioned in Welch as suitable for acute migraine treatment and migraine prophylaxis would not be used interchangeably by the skilled artisan in the treatment of these very different indications. It cannot, therefore, flow from the teachings of Welch that any of the other compounds featured for migraine prophylaxis would be sucessfully used in acute migraine treatment.

Even the Examiner's reliance on Walser for teaching the "parenteral mode of administration of valproate" is flawed. Appellants respectfully submit that just because Walser discloses that "an 800 mg dosage of sodium valproate administered by intravenous injection suppressed serum cortisol levels in normal subjects" (see Walser, column 4), that one skilled in the art would *not* combine Welch and Walser in order to "get the valproate quicker to the blood stream" to treat acute migraine. First, the effective dose in reducing the production of glucocorticoid related to chronic renal failure has nothing to do with the treatment of either acute migraine or even preventative migraine. Second, as shown in Welch, *intravenous* administration of drugs for the treatment of acute migraines is not always considered the most effective. For instance, sumatriptan is most effective when given subcutaneously or orally, not intravenously. (See Welch, p. 1478). Ergotamine, on the other hand, is "best absorbed rectally," and again, not intravenously. (See Welch, p. 1478). Therefore, one skilled in the art at the time of the invention would not be motivated to use a recommended dosage and form of administration for the reduction of glucocorticoid production in treating acute migraine.

Appellants respectfully submit that the Examiner has misconstrued what the references teach, and as such the prior references, alone or combined, do not teach or suggest all the claim limitations. Appellant also submits that, at the time the invention was made, there was no motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references to arrive at the use of an intravenous administration of valproate for the

abortive treatment of acute migraine headache. Appellant further submits that one of ordinary skill in the art would not have had a reasonable expectation of success in attempting to combine the prior art references to arrive at the claimed invention, at the time the invention was made. In conclusion, the combining of references that teach the use of valproate in the prevention of migraine, which involves different mechanisms and receptors than acute migraine, and the intravenous administration of valproate for the treatment of chronic renal failure lacks motivation. The motivation cannot simply be to "get the valproate quicker to the blood stream". Under this reasoning, one who is not even skilled in the art could combine a drug indicated for one disease with the form of administration for a totally unrelated disease and have an effective drug for a third disease, completely unrelated to other two. However, at the time of this invention, one skilled in the art, with the knowledge that the mechanism of action of valporate, although not known but hypothesized to act on mechanisms related to the prevention of migraine, would understand and appreciate the differences in the mechanisms and receptors involved in the prevention of migraine and in the treatment of acute migraine and simply not blindly use valproate for the treatment of acute migraine.

In view of all of the foregoing, Appellants respectfully submit that the intravenous administration of valproate for the treatment of acute migraine of the instant invention is patentable over the art of record and that no motivation exists to combine the references.

CONCLUSION

Appellants submit that pending claims 1-14 are patentable and it is respectfully submitted that the Board reverse the final rejection of these claims for the reasons set forth above.

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